REMARKS

Claims 1-11 are presently under consideration. In view of the restriction requirement imposed by the Examiner, Applicant cancels claims 12-14 without prejudice. Claim 1 has been amended to correct a typographical error. Claims 1, 5, 6, 9, and 10 have been amended to more particularly point out and distinctly claim what Applicant regards as his invention. Specifically, claims 1 and 10 have been amended to clarify that "probe" is a DNA fragment of defined sequence. Since from the specification, probe means a DNA fragment, this is not a narrowing amendment. Moreover, support for the amendments can be found at page 7, lines 20-21 and Figure 2 and as such, the amendments do not constitute introduction of new matter. Claims 5 and 6 have been amended to correct a typographical error. Applicant reserves the right to prosecute the subject matter of claims 12-14 and originally filed claims 1, 9, and 10 in one or more related applications. For the Examiner's convenience, the pending claims are attached hereto as Exhibit B.

Rejection Under 35 U.S.C. § 112, Paragraph 2 Should Be Withdrawn

Claims 1-9 have been rejected under 35 U.S.C. § 112, paragraph 2 as being indefinite because the phrase "the base change" is non sequitur. Applicant submits that claim 1 has been amended to correct a typographical error such that part (d) of claim 1 recites in relevant part "...location of the base change" rather than "...location the base change." As such, Applicant respectfully submits that the correction of the typographical error obviates the Examiner's rejection of claim 1 and its dependent claims 2-9 and requests that the rejection of claims 1-9 under 35 U.S.C. § 112, paragraph 2, be withdrawn.

Rejection Under 35 U.S.C. § 102(e) Should Be Withdrawn

Claims 1-7 and 9 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Cotton *et al.* (United States Patent No. 5,958,692; "the '692 patent"). Preliminarily, Applicant notes for the record that the '692 patent is a continuation of United States Patent No. 5,5,698,400 ("the '400 patent") which issued December 16, 1997, more than a year prior to the earliest claimed priority date of the instant application. However, because the '692 patent and the '400 patent have identical disclosures, Applicant submits that the arguments made herein with respect to the '692 patent would also be equally applicable to

the '400 patent. Indeed for the following reasons, Applicant submits that claims 1-7 and 9 are patentable over the '692 patent or the '400 patent.

To anticipate, a reference must disclose every element of the claims. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Although the Examiner asserts that the '692 patent teaches a method of detecting base changes in a nucleic acid of interest comprising all of the limitations recited in claims 1-7 and 9, Applicant respectfully disagrees.

Claim 1 and its dependent claims 2-9 are directed to a method of detecting base changes in a nucleic acid using a number of specific steps. In particular, the method contemplated by claim 1 requires that the detection of the presence of a base change is achieved by detection of a DNA fragment of defined sequence ligated to the resulting cleaved heteroduplex. The '692 patent does not teach such a method of detecting a base change. Rather, the '692 patent reports the detection of mutations in a DNA fragment by digestion with resolvase followed by electrophoresis. The detection of 2 or more DNA fragments instead of a single fragment found in the control undigested DNA indicates the presence of one or more mutations in the target DNA. To facilitate the fragment detection, the DNA, before or after digestion with resolvase, can be labeled at one end by a radioactive tracer, digoxgenin, biotin, fluorescent dye or other standard labeling method (*see* col. 4, ll. 54-63). In contrast, in claims 1 and 2-7 and 9 of the instant application, the detection of base changes at the site of enzymatic digestion of mismatches is achieved by ligation of a DNA fragment of defined sequence. In particular, the sequence of the DNA fragment allows the identification of base changes as well as the exact location of the base changes, as indicated by the site of fragment ligation into the nucleic acid. In contrast, the '692 patent does not mention or even suggest the ligation of a fragment of DNA at the site of mutation.

The detection of base changes by detecting the ligation of a DNA fragment of defined sequence as set forth in the methods of claims 1-9 offers a number of advantages that cannot be achieved by the method disclosed in the '692 patent. The claimed methods allow an accurate localization of the base change in a gene sequence of any size. In contrast, the '692 patent only discloses a method for determining the position of a mutation based on DNA size estimation of the cleaved heteroduplex fragments by electrophoresis which can be achieved accurately only when the fragments to be analyzed are less than 2 kb. The claimed methods require only the presence of a base change that allows for cleavage and ligation of

the DNA fragment and does not require any sequence knowledge of the nucleic acids to be analyzed. In contrast, the '692 patent method is useful only if the sequence analyzed for mutations is a known sequence.

Moreover, the methods contemplated by the claimed invention can be used to identify, in one step, mutations in multiple nucleic acids. For example, where the methods are performed within a plasmid cDNA library, screening with the ligated DNA fragment will identify all the genes containing the DNA fragment and implicitly the base change(s) in all of the members of the library. Thus the methods detect in one step, the base changes in multiple genes (usually several thousands). In contrast, the method described in the '692 patent can only be used for detecting a mutation in a single DNA fragment.

The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

The Examiner has also rejected claim 10 under 35 U.S.C. § 103(a) as obvious over the '692 patent. In particular, the Examiner alleges that the '692 patent provides a kit for detecting base changes in a nucleic acid of interest comprising the steps recited in claim 10 and that it would be obvious to include in the kit a means for detecting the ligated probe. Applicant submits that in view of the foregoing reasons enumerated *supra*, that the method of claim 1 is patentable, the kit of claims 10 and 11, containing the components for a method very different from the '692 patent method is likewise not obvious over the '692 patent. Accordingly, please withdraw the rejection.

The Objection to Claim 8 Should Be Withdrawn

The Examiner has objected to claim 8 because the claim is dependent upon a rejected independent base claim. In view of the foregoing, Applicant respectfully submits that because the rejection of independent claim 1 should be withdrawn, the objection of claim 8 is obviated.

CONCLUSION

Applicant respectfully requests that the present remarks and amendments be made of record in the instant application. An early allowance of the application is earnestly requested. As Applicant's attorney, Margaret Brivanlou, discussed with the Examiner on

January 29, 2003, the Examiner is respectfully invited to telephone her at (212) 790-6424 to discuss any outstanding issues in connection herewith.

Respectfully submitted,

Date: February 3, 2003

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EXHIBIT A
MARKED-UP VERSION OF AMENDED CLAIMS
APPLICATION SERIAL NO. 09/808,504

1. (amended) A method for detecting base changes in a nucleic acid of interest which comprises the following steps:

(a) contacting the nucleic acid of interest with a suitable reference nucleic acid under suitable conditions such that the nucleic acid of interest forms a heteroduplex with the reference nucleic acid;

(b) contacting the heteroduplex with a suitable nuclease or a combination of suitable nucleases so as to selectively cleave the heteroduplex at a position of a base change on the nucleic acid of interest with respect to the reference nucleic acid;

(c) ligating a [detectable probe] DNA fragment with a defined sequence to the cleaved heteroduplex; and

(d) detecting the ligated [probe] DNA fragment under suitable conditions so as to determine the presence and location of the base change.

5. (amended) The method of [claims] claim 1 wherein the reference nucleic acid is DNA.

6. (amended) The method of [claims] claim 1 wherein the reference nucleic acid is a circular nucleic acid.

9. (amended) The method of claim 1 wherein the [detectable probe is a nucleic acid] DNA fragment has the sequence set forth in figure 2.

10. (amended) A kit for detecting base changes in a nucleic acid of interest which comprises the following components:

(a) a suitable reference nucleic acid capable of forming a heteroduplex with the nucleic acid of interest;

(b) a suitable nuclease or a combination of suitable nucleases capable of selectively cleaving the heteroduplex at a position of a base change on the nucleic acid of interest with respect to the suitable reference nucleic acid;

(c) a [detectable probe] DNA fragment of defined sequence capable of being ligated to the cleaved heteroduplex; and

(d) a means to detect the ligated [probe] ligated DNA fragment.